

Variant: *NM_001313913.2:c.1245G>A*

Version: 1.0

CA414447533 [↗](#)

Gene: F9 ([HGNC:2158](#))

Condition: hemophilia B ([MONDO:0010604](#))

Inheritance Mode: X-linked inheritance

UUID: 63fb42c1-a20e-439a-a083-1172c25353eb

Approved on: 2024/4/26

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HGVS expressions

NM_001313913.2:c.1245G>A

NC_000023.11:g.139562044G>A

CM000685.2:g.139562044G>A

NC_000023.10:g.138644203G>A

CM000685.1:g.138644203G>A

NC_000023.9:g.138471869G>A

NG_007994.1:g.36309G>A

ENST00000218099.7:c.1359G>A

ENST00000643157.1:n.1723+303G>A

ENST00000218099.6:c.1359G>A

ENST00000394090.2:c.1245G>A

NM_000133.3:c.1359G>A

NM_001313913.1:c.1245G>A

NM_000133.4:c.1359G>A

Pathogenic

Met criteria codes **5**

PP4_Moderate

PS4

PVS1_Moderate

PM6

PM2_Supporting

Evidence Links **0**

Expert Panel

[Coagulation Factor Deficiency VCEP](#) [↗](#)

Criteria Specification Information

[↗](#) **Criteria Specification:** *ClinGen Coagulation Factor Deficiency Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for F9 Version 1.0.0*

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Coagulation Factor Deficiency VCEP

The variant c.1359G>A (p.Trp453Ter) introduces a premature stop codon in the last exon and is predicted to result in a truncated protein with more than 90% of the protein intact. This variant has been reported in at least 5 probands with severe hemophilia B, including as a de novo occurrence with assumed maternity and paternity, meeting phenotypic criteria for F9 (PMID: 36347023; PMID: 10698280; PMID: 8091381; PMID: 29296726). This variant is absent from males in population databases (gnomAD v2.1.1/gnomAD v3). In summary, this

variant meets the criteria to be classified as pathogenic. ACMG/AMP criteria are applied, as specified by the Coagulation Factor Deficiency Variant Curation Expert Panel for F9: PVS1_moderate + PM2 supporting + PS4 + PP4_Moderate. (ClinGen Coagulation Factor Deficiency Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for F9 Version 1.0.0, Released 10/5/2023).

Met criteria codes

PP4_Moderate			Patient from MLOF/Versiti cohort with severe FIX (MLOF does del dup and sequencing)
PS4			Refresh 4/2/24: This variant been reported in at least 5 probands (>4 probands & 0 gnomAD alleles) meeting phenotypic criteria for F9 (PMID: 36347023; PMID: 10698280; PMID: 8091381; PMID: 29296726) Probands counted: Wulff 2, MLOF 1, Saad 1, Liu 1 which is greater than 4, upgraded to PS4 Strong 3 Hemophilia B patients from PMIDs: 10698280 and 8091381 meet F9 phenotype criteria, meeting PS4_Moderate
PVS1_Moderate			Refresh 4/2/24: Previously applied PVS1 strong (I think because peptidase domain met PM1), I downgraded to PVS1_mod because PM1 can no longer be applied to peptidase domain and this premature stop codon results in 2% truncation of protein (452/461). The nonsense variant occurs in the last exon and NMD is not predicted. The residue falls within amino acid positions 227-459 encoding the Peptidase S1 domain, which is recognized as a region critical to protein function by the CFD VCEP. Therefore, PVS1_Strong is applied.
PM6			1 Hemophilia B patient from PMID: 30648777 meets criteria for PM6
PM2_Supporting			The variant is absent from gnomAD v2.1.1 and v3 and meets criteria for PM2_Supporting

Curation History



 

 

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